Orchid BioSciences (formerly Molecular Tool, Inc.)

# Integrated Microfabricated Devices for DNA Typing

*Genetic analysis is the study of DNA to determine information relating to identity or disease. Studying the subtle changes in genes when a cell becomes diseased offers opportunities to search for new molecular targets for drugs. Genetic analysis promises to provide more accurate diagnoses and customized drug therapies. In 1994, genetic analysis was cumbersome and expensive, with each test costing approximately $100. Molecular Tool, Inc. was an innovative start-up company with a desire to improve genetic analytical testing for human health. The company had already developed practical applications for thoroughbred horse genetics and wanted to apply improved techniques for human genetic analysis. Molecular Tool intended to automate and simplify analyses by creating a miniature "lab on a chip." If successful, they could reduce cost and space requirements from a manually operated 20-foot x 15-foot laboratory, down to an automated 1-square-inch glass chip. Industry analysts predicted that affordable genetic analyses could be performed on desktop systems, but technical risks included placing microscopic samples on the chip, taking images of the samples, and analyzing those images. Molecular Tool applied for funding from the Advanced Technology Program (ATP) under the "Tools for DNA Diagnostics" focused program in 1994.*

*ATP awarded cost-shared funding for a three-year project, beginning in 1995. Molecular Tool successfully developed a patented prototype single nucleotide polymorphism (SNP) analysis tool in 1998. (SNPs, or "snips" are useful genetic markers or places in the genetic code that detect minute variations in the DNA sequence.) Orchid BioComputer (later renamed Orchid BioSciences) purchased Molecular Tool that year and acquired the ATP-funded lab on a chip technology. Following further development, Orchid reduced the cost of a typical DNA analysis by approximately 70 percent and increased accuracy to 1 in several billions statistical probability from 1 in a million. The company continued enhancing the technology and commercialized its SNPstream Genotyping System, as well as providing SNP analyses on a fee-for-service basis by 2001. Orchid acquired three identity genomics testing competitors and became a leading provider for the forensic and paternity DNA testing markets. In 2002, the company decided to focus on its DNA analysis services business and sold its SNP genotyping business, which included an exclusive license to Orchid's SNP analysis technology, to Beckman Coulter, a leading provider of tools for clinical laboratories. Beckman continues to market and improve the SNPstream Genotyping System, based on ATP-funded technology, while Orchid focuses its efforts on fee-for-service genetic analyses. Orchid had sales in excess of $62 million in 2004. The global DNA diagnostics industry is expected to grow from $1 billion in 2003 to $6 billion by 2010.*

**COMPOSITE PERFORMANCE SCORE**
(based on a four star rating)
* * * *

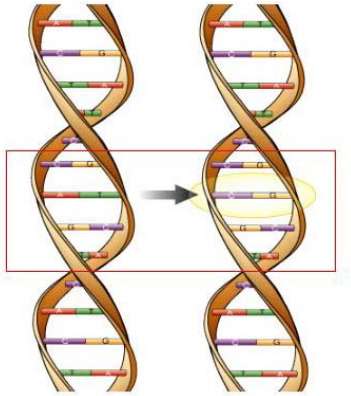
**Research and data for Status Report 94-05-0034 were collected during June – August 2004.**

## Genetic Analysis Is Cumbersome and Costly

In the early 1990s, Molecular Tool, Inc. was a small Maryland biotechnology company of highly skilled microbiologists that wanted to develop advanced genetic applications. Located near a racetrack, Molecular Tool received its first commission to perform advanced genetic testing for thoroughbred racehorses. The company had developed a proprietary genotyping biochemistry, which it called Genetic Bit Analysis (GBA)

to identify and analyze variations in the individual bases of DNA. Molecular Tool used GBA to verify horse parentage and, in 1994, generated more than 500,000 individual horse genotypes.

In DNA sequencing, the scientist looks at a long string of DNA and identifies fragments that determine identity or information relating to disease. The most common type of DNA sequence variation is the single nucleotide polymorphism (SNP, or “snip”), a place in the genetic code where DNA differs from one person to the next by a single letter (see illustration below). The human genome contains more than 2 million SNPs. The genetic code is specified by the four nucleotide "letters": A (adenine), C (cytosine), T (thymine), and G (guanine). A SNP occurs when a single nucleotide (A, T, C, or G) in the genome sequence is mismatched. The analyst unzips the DNA sample and looks at one side. For example, in the illustration below, the left side of the first highlighted DNA sequence shows C**A**GT. The second SNP variation shows C**C**GT. For a variation to be considered a SNP, it must occur in at least 1 percent of the population. For example, a place in the genome where 93 percent of the population has a T and the remaining 7 percent has an A is a polymorphism. SNP scoring (analysis) is simpler than complete DNA sequencing.



Example of a SNP variation. An individual DNA sequence varies from the general population by one nucleotide. Small changes in DNA sequence such as these can affect drug response and disease susceptibility. Reproduced with permission from BioTeach http://bioteach.ubc.ca.

Certain SNPs may predispose some people to a particular disease, and this may explain why some respond better to certain drugs. When a SNP occurs, the gene’s function may change; for example, it may cause the individual to develop a bacterial resistance to antibiotics. SNPs can identify differences in drug metabolism between individuals; they can pinpoint which patients may not respond to a drug or may suffer an adverse drug response. Furthermore, SNPs can also be used in genetic diagnosis to uniquely identify individuals; for example, to link a defendant to the crime scene in a criminal case. Analysts predicted that genetic analyses could some day be performed by affordable desktop systems in clinics and physicians’ offices. These analyses would make more accurate customized diagnoses and even predict disease to facilitate preventive medicine.

Technology available in 1994 required several hundred to several thousand test-tube tests to decode essential elements among the 3 billion bits of information that make up the human genetic code. Performing 1,000 genetic tests to uniquely identify one human sample (or to test for disease) required at least two lab technicians, a 20-foot by 15-foot laboratory, several machines to perform rote tasks, and 12 hours of time, at a cost of $100 or more per test.

Molecular Tool sought opportunities to advance DNA testing for human healthcare by optimizing and dramatically miniaturizing existing tools. The company aimed to identify the top 1,000 human SNPs that contribute to the lack of efficacy in drugs, adverse side effects, and predisposition to disease.

## Molecular Tool Proposes to Miniaturize Biotechnology

Reducing the size of the lab components to fit onto a chip would lower cost through reduced chemical use, increased automation, and greater efficiency. Molecular Tool’s goal was to compress most of the functions of SNP analysis that were being done in the 20-foot by 15-foot biotechnology laboratory onto a 1-square-inch glass chip. In the same way that a computer chip manipulates electrons through microscopic wires, biotechnology chips would manipulate fluids along microscopic channels in order to search the DNA strands for SNP variations. A subcontractor, Naval Research Laboratories, would assist with the microfluidics technology. They would develop stamping methods to create patterned DNA surfaces and a film-patterning approach to validate Molecular Tool’s optical-scanning system.

Molecular Tool submitted a proposal to ATP in 1994 under the focused program, “Tools for DNA

Diagnostics," and was awarded cost-shared funding for a three-year project beginning in 1995. If successful, Molecular Tool hoped that the miniaturized tool would make comprehensive DNA diagnostics routinely available at a low cost. The new tool would improve genotype processing power more than a hundredfold; moreover, dramatic reductions in cost would make DNA testing more accessible. This, in turn, could support preventive medicine by providing valuable information to people who are genetically predisposed to certain diseases. Preventive disease management could reduce healthcare costs over time.

Molecular Tool faced significant technical risks. Liquids behave very differently in minute quantities; activities such as heating, mixing, and separating fluids would be unpredictable. Challenges included developing the necessary techniques for micromachining and for handling fluids on a microscopic scale. One of the key challenges was to find ways to move tiny amounts of fluid through channels etched on the glass chip. Although primitive versions of analytical devices had been constructed on microchips, integrated microinstrumentation was a new field. Multiple processing steps had never been integrated on a single chip. In addition, when moving strands of DNA, another challenge occurs: the oligonucleotides (short single strands of DNA) might not behave as expected due to chemical sensitivity. Molecular Tool focused their research on two principal objectives: first, to develop a microanalytic device to perform SNP analysis on single genetic bits; and second, to demonstrate the feasibility of creating a microdevice capable of analyzing 100 SNPs.

## Miniaturized and Automated Instruments to Speed Processing

Molecular Tool encountered several technical challenges in developing their strategy of miniaturization and integrated automation, in which they would adapt a proven genotyping biochemistry to micromachined instruments and microfluidic processing. Their technical challenges included the following:

- Reduce labor requirements by achieving higher throughput (larger sample quantities)
- Reduce the cost of biochemicals by processing smaller samples and reducing reagent consumption
- Reduce processing complexity by miniaturizing and combining equipment

A carefully prepared sample, such as drops of blood, would be put on a glass chip, where channels etched on the chip would direct the liquid in a manner similar to circuits directing electricity in computers. As the blood passed through different routes, reagent chemicals would extract genetic material and, through a chemical process known as amplification, would make many copies of the material so multiple genetic tests could be performed. Various reagent chemicals applied to the chip would react with the genetic material in the sample. A laser would then be used to detect which chemicals had been absorbed, and advanced software would be used to interpret the chip data results. From this analysis, scientists could determine the genetic "fingerprint" of the sample. In another application of the technology, a doctor could determine if the patient carried genes linked to a variety of illnesses.

***Molecular Tool's goal was to compress most of the functions of single nucleotide polymorphisms analysis that were being done in the 20-foot by 15-foot biotechnology laboratory onto a 1-square-inch glass chip.***

Molecular Tool's ultimate goal was to reduce the size of genotyping tools 1,000-fold over their existing tools. Moving tiny amounts of sample material short distances in minute channels would result in deep reductions in reagent consumption.

Molecular Tool's proposed system had three main components:

- Micromachined analytical instruments in glass (the chip) would be built with photolithographic methods (photographic process used to transfer circuit patterns) on a sub-millimeter scale
- Electro-osmotic pumping (moving liquid through a semi-permeable membrane) would precisely measure nanoliter volumes of sample material (a nanoliter is one-billionth of a liter), mix reagents, and allow the material to interact with sensitive fluorescence detection systems

- Fluorescent dye would attach to specific cells, and researchers would measure the fluorescent signal at specific probe locations to detect the genes

Molecular Tool's plan was to reduce the size of sample testing sectors, or wells, from 1 square centimeter down to less than 1 square millimeter. After developing an early prototype, the company would integrate the tools, automate them, and increase throughput. Ultimately, their goal was to shrink the entire genotyping lab to the size of a 1-square-inch microchip.

## ATP-Funded Project Achieves All Technical Goals

At the conclusion of the project in 1998, Molecular Tool had successfully converted existing SNP analysis technologies into a miniaturized format to create a high-throughput and economical DNA analysis of disease states and forensic identification (DNA fingerprinting). The company fabricated DNA microarrays, "printing" an orderly arrangement of DNA fragments that represented the genes onto the glass slide for analysis. Each DNA fragment representing a gene was assigned a specific location on the array. DNA or RNA in the overlaid sample attach (through a process called hybridization) to a complementary spot on the array; that is, Gene-A will stick to a spot composed of a Gene-A fragment. Molecular Tool developed high-resolution optics in order to see patterns in tiny sizes. They scanned the fluorescent-labeled (hybridized) microarrays, looking for SNP variations, and relied on robotics to increase analysis speed. Each glass chip had an array with 384 wells, which was an increase from 96 wells at the start of the project. Molecular Tool achieved 100 percent of their technical goals and developed a working prototype tool to identify and validate SNPs, sometimes referred to as SNP scoring. They were awarded five patents for their advances and published their findings in academic journals. ATP funding was critical to developing this SNP scoring technology.

## Technical Success Gains Commercial Attention

In 1998, Molecular Tool was purchased by Orchid BioComputer, located in Princeton, NJ. The strategy underlying the acquisition was the combination of Orchid's high-throughput microfluidics technology with Molecular Tool's proprietary SNP analytic chemistry and GBA capabilities to create even faster, more flexible tools to analyze correlations between SNPs and specific genotypes, diseases, and therapeutics. Commenting on the Molecular Tool acquisition in 1998, Dale Pfost, Ph.D., Orchid's then-CEO, said, "The genetic variations expressed in SNPs are the foundation of pharmacogenomics and pharmacogenetics. The pharmaceutical industry has expressed great interest in targeting subgroups of patients based on their individual genetic differences to improve therapy through the use of existing drugs and the development of new drugs that have greater efficiency and fewer side effects than those available today. Companies can use the [SNP] platform as a rapid and cost-effective way to assess disease correlation and … responses to different drugs."

Orchid's efforts to combine Molecular Tool's analysis technology with its microfluidics platform enabled Orchid to focus on developing automated high-throughput instrument systems, including the automation of sample preparation. Orchid later added a microscope with a digital camera to the SNP analysis tools to more easily read results.

## Orchid Commercializes SNP Technology

In 1999, a group of pharmaceutical and biotechnology companies formed a consortium, called The SNP Consortium Ltd. Together the companies invested $45 million, with the goal to produce a map of the human genome. At the same time, Orchid opened a new SNP genotyping facility to house labs devoted to microfluidic chips, chemistry, and optics. The consortium contracted with Orchid to use this facility to identify up to 300,000 SNPs and to "map" at least 150,000, or determine their location within the human genome; the consortium would provide this information to the public free of charge. Furthermore, the consortium wanted Orchid to test identified genetic markers. Orchid used its SNP genotyping tools and GBA software developed during this project to perform the genotyping assays.

## Medical Groups Use SNP Technology to Study Disease and Treatment

Also in 1999, Orchid began scoring SNPs for medical applications. The company joined with the University of Washington's School of Medicine to perform high-

throughput SNP genotyping to study genetic variability, its relationship to the onset of disease, and pharmaceuticals. Moreover, Orchid's genotyping was being used at the Mayo Clinic to determine whether patients under- or over-metabolize drugs so that drug dosage could be more carefully tailored to the patient.

## SNPstream Product Enters the Market

In cooperation with Luminex Corp., Orchid used the ATP-funded technology to develop SNPstream, an affordable, rapid-throughput system for performing SNP scoring. The system combined Luminex's LabMAP system with Orchid's proprietary line of SNPware reagent kits. In 1999, the SNPstream system was able to score thousands of SNPs per day.

By the end of 2000, Orchid could score a million SNPs per day, with the goal of finding and patenting clinically important relationships between SNPs and pharmaceuticals. The ultimate goal was to improve drug treatment options to fight disease. The company offered a successful initial public offering that year and changed its name to Orchid BioSciences.

*"The genetic variations expressed in SNPs are the foundation of pharmacogenomics and pharmacogenetics."*

In 2001, Orchid entered the market with its SNPstream ultra-high throughput, array-based genotyping system (see illustration), which was based on the ATP-funded technology. The system was capable of handling more than 800,000 genotypes per day. SNPstream analyzes up to 100,000 data points for increased accuracy (in 1994, Molecular Tool had been testing only 1,000 data points). Furthermore, a typical result showed 1 in several billions statistical probability, increased from 1 in a million. Total cost for the processing of sample of DNA had been reduced by approximately 70 percent, and labor involved in processing had been reduced by approximately 75 percent. The entire process of DNA testing which previously took up to 4 weeks, could now be completed in about a week. At the same time, the company began to conduct genetic analysis on a fee-for-service basis for the biotechnology and pharmaceutical companies, as well as academic laboratories.

A technician reads results from the automated, scalable SNPstream genotyping system, which includes a robotic analysis instrument and computer readout.

## Orchid Expands and Licenses Its Technology

Orchid's success with SNP technology allowed the company to expand and license its technology to other laboratories, which could adapt the technology to their instrument platform. By 2001, Orchid acquired three more companies that provided compatible identity genomics testing: GeneScreen, Inc., Lifecodes Corp., and Cellmark Diagnostics (a subsidiary of AstraZeneca, which had pioneered the introduction of DNA testing for paternity and forensic analyses in the United Kingdom). Orchid granted several SNP-related non-exclusive licenses to use its proprietary SNP technology to Applied Biosystems, Amersham Pharmacia Biotech, and Quest Diagnostics, as well as an exclusive license to PerkinElmer to use Orchid's SNP technology to perform fluorescence-based analyses.

## Orchid Refocuses on DNA Services

By the end of 2002, four years after the ATP-funded project ended, Orchid was concentrating on its highly successful DNA services business and had moved away from product development, customization, and sales. Beckman Coulter, a leading provider of instrument systems for life sciences and clinical laboratories, purchased the instrumentation piece of Orchid's business, to continue to develop and offer SNP scoring systems and consumables to the research market. Beckman began producing and selling reagent kits, software, and systems globally. Beckman, by virtue of its exclusive license from Orchid, incorporated Orchid's proprietary SNP-identification technology

for performing SNP analyses on DNA sequencers, microarray plates, and flow cytometers. "Our collaborative efforts with Orchid enhance our offerings to important segments of the marketplace and are a key strategic element in our genomics program," said George Bers, President of Life Science Research for Beckman Coulter.

Orchid continues to be a leading provider of identity genetics services for the forensic and paternity DNA testing markets. Their work includes parentage testing to aid child support enforcement agencies, criminal casework analysis, DNA testing for convicted offender DNA databases, casework for law enforcement laboratories, the identification of victims of accidents, and consulting services for attorneys. Orchid's SNP technology was used in collaboration with the New York Office of the Medical Examiner in an attempt to identify the large number of World Trade Center victims for whom conventional identification methods had failed. Orchid has forensic contracts with major metropolitan police departments, such as Los Angeles and Houston, as well as with London's Scotland Yard. In 2003, the Federal Bureau of Investigation awarded Orchid two contracts to develop SNP technology for advanced forensic applications to identify individuals using degraded DNA samples. Orchid also offers a premium "DNA Express Service" to help law enforcement agencies analyze backlogs of DNA evidence from unsolved crimes. DNA Express provides forensic DNA analyses in five business days compared with the standard four to five weeks.

Orchid continues to develop new applications for uses of its SNP technology, as it has to conduct global disease testing programs. For example, in 2002, Orchid was awarded a contract by the Department of Environment and Rural Affairs in the United Kingdom to help selectively breed disease out of the sheep population. The company processes samples for the United Kingdom's pioneering sheep genotyping program to help farmers use selective breeding to eliminate the disease scrapie from their flocks. Scrapie is a progressive brain disease in sheep that causes itching so intense that the animals scrape off their wool. In 2003, Orchid analyzed nearly 500,000 samples for scrapie susceptibility and has genotyped more than 1.4 million sheep to date. Orchid's contracts in forensic, paternity, and animal testing have led to financial success for the company. Identity genetics accounted for 97 percent of Orchid's 2003 revenues, or $49 million. Total sales grew 23.5 percent in 2004 to $62.5 million.

## Genomics Is Growing Globally

Genomics is still an emerging technology growth area. Relying on the original ATP-funded technology concepts, Orchid BioSciences and Beckman Coulter are well positioned for continuing expansion in the diagnostic tool industry. Global molecular diagnostics spending has risen from $78 million in 1994 to $1 billion in 2003, and it is expected to reach $6 billion by 2010. Genomics research spending is expected to increase from $4.5 billion in 2000 to $7 billion in 2010 (Andrew Broderick, Genomics, SRI Business Intelligence, 2003, p. 41, 48).

## Conclusion

As a result of funding provided by ATP, Molecular Tool, Inc. successfully developed a prototype lab-on-a-chip single nucleotide polymorphism (SNP) analysis tool for DNA testing. They were able to shrink the space requirement for DNA analyses from a 15- x 20-foot laboratory to a 1-square-inch chip. In addition, they achieved comparable reductions in labor, time, and chemical reagent use. The company was awarded five patents for its technology advances and published its findings. When Orchid BioSciences bought the company and its ATP-funded SNP analysis system in 1998, it continued development. Following project conclusion in 1998, Orchid built a large SNP scoring laboratory in 1999 and began analyzing large numbers of samples. The company began marketing its SNPstream analysis system in 2001. In 2002, Orchid sold the instrumentation portion of this business to Beckman Coulter, a leading instrument manufacturer in the biotechnology industry. As of 2004, Beckman continues developing and marketing SNPstream, based on ATP-funded technology, which is capable of performing more than 800,000 genotypes per day. Orchid, which provides DNA analyses to multiple markets, continues to find new uses for its SNP detection technology, and most recently earned $62.5 million in sales in 2004.

# PROJECT HIGHLIGHTS
# Orchid BioSciences (formerly Molecular Tool, Inc.)

**Project Title:** Integrated Microfabricated Devices for DNA Typing

**Project:** To scale the size of the company's state-of-the-art Genetic Bit Analysis (GBA) technology down by a factor of 1,000, developing the necessary techniques for micromachining and for handling fluids on a microscopic scale to make a simple, compact DNA typing instrument.

**Duration:** 2/15/1995 – 2/14/1998
**ATP Number:** 94-05-0034

## Funding (in thousands):

| | | |
|---|---|---|
| ATP Final Cost | $1,940 | 74% |
| Participant Final Cost | $ 684 | 26% |
| Total | $2,624 | |

**Accomplishments:** With ATP funding, Molecular Tool succeeded in developing a miniaturized DNA analysis instrument that reduced the cost and required laboratory space. The project met 100 percent of its goals. Accomplishments include:

- Molecular Tool developed a functioning prototype single nucleotide polymorphism (SNP) detection and analysis tool.
- The prototype device contained 384 reaction sectors, or wells, which was an increase from 96 wells at the start of the project in 1994.
- Orchid BioSciences purchased Molecular Tool in 1998 and integrated advanced microfluidics and optics, including a digital camera to improve analysis.
- Orchid's SNP analysis instrument, called SNPstream, performs more than 800,000 DNA analyses per day.

In addition, Orchid developed commercial applications for SNP technology:

- The SNP technology was used in identifying the remains of some New York City World Trade Center victims, which could not be identified by conventional DNA analysis due to sample degradation.
- Orchid has contracts with major metropolitan police departments for forensics, including Los Angeles, Houston, and London's Scotland Yard. They also developed advanced forensic applications to identify individuals from unsolved crimes using degraded DNA samples for the Federal Bureau of Investigation. Their DNA Express service provides forensic DNA analyses in five business days compared with the standard four to five weeks.
- Orchid collaborated with the University of Washington's School of Medicine to study genetic variations, the onset of disease, and pharmaceuticals.
- Orchid collaborated with the Mayo Clinic to tailor drug dosage based on whether patients under- or over-metabolize drugs. This is just the beginning of such improvements in medical treatment based on pharmacogenetics.
- Orchid analyzed SNPs for the United Kingdom's scrapie genotyping program to help sheep farmers use selective breeding to eliminate the disease scrapie from their flocks. The company has genotyped nearly 1 million sheep to date.

Molecular Tool filed six patent applications from this ATP-funded project, of which the following five were awarded:

- "Covalent attachment of nucleic acid molecules onto solid-phases via disulfide bonds"
  (No. 5,837,860: filed March 5, 1997; granted November 17, 1998)
- "Attachment of unmodified nucleic acids to silanized solid phase surfaces"
  (No. 5,919,626: filed June 6, 1997; granted July 6, 1999)
- "Covalent attachment of nucleic acid molecules onto solid-phases via disulfide bonds"
  (No. 6,030,782: filed November 21, 1997; granted February 29, 2000)
- "De novo or 'universal' sequencing array"
  (No. 6,322,968: filed November 21, 1997; granted November 27, 2001)
- "Covalent attachment of unmodified nucleic acids to silanized solid phase surfaces"
  (No. 6,136,962: filed June 23, 1998; granted October 24, 2000)

# PROJECT HIGHLIGHTS
## Orchid BioSciences (formerly Molecular Tool, Inc.)

**Commercialization Status:** After acquiring Molecular Tool in 1998, Orchid BioSciences developed a thriving DNA analysis service business based on its SNPstream genotyping system and commercialized it in 2001. Beckman Coulter purchased the instrumentation from Orchid in 2002 and continues to sell the system. Orchid is a leading product and service provider of DNA forensic and paternity services, based on the ATP-funded SNPstream system:

- **Product**: SNPstream Ultra High Throughput (UHT) is an automated array-based genotyping tool. It entered the market through Orchid BioSciences in 2001. The business pertaining to the production of the SNPstream instruments and consumables was sold to Beckman Coulter in December 2002. Beckman also has an exclusive license from Orchid for the use of SNP identification technology for use with the system. As of 2004, Beckman continues to develop and enhance the system, marketing to research and clinical laboratories.

- **Service**: Orchid BioSciences provides genetic analyses using SNPstream UHT on a fee-for-service basis (for biotech companies, pharmaceutical companies, and criminal justice agencies). Orchid's facility was providing up to 1 million SNP scores per day by the end of 2000 on a fee-for-service basis. Sales exceeded $1 million the first year and exceeded $62 million in 2004.

**Outlook:** SNP scoring plays a key part in the evolving DNA diagnostics industry. The outlook for integrated microfabricated devices and services related to DNA typing is excellent. Uses include paternity testing, forensic testing, and pharmacogenetic testing. The global market reached $1 billion in 2003 and is projected to reach $6 billion by 2010. It is hoped that further testing will ultimately lead to customized drug treatments based on patients' unique DNA.

**Composite Performance Score:** * * * *

**Number of Employees:** 20 employees at project start, 60 as of February 1998 (at project end, Molecular Tool); 430 as of December 2003 (Orchid BioSciences).

**Focused Program:** Tools for DNA Diagnostics, 1994

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Naval Research Laboratory
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**Publications:** Molecular Tool and Orchid BioSciences shared knowledge through the following publications:


- Head, S. R., P. Parikh, Y.-H. Rogers, W. R. Bishai, P. Goelet, and M. T. Boyce-Jacino. "Nested Genetic Bit Analysis (N-GBA) for Mutation Detection in the p53 Tumor Suppressor Gene." *Nucleic Acids Research*, Vol. 25, No. 24: 5065-71, 1997.
- Head, S. R., P. Parikh, Y.-H. Rogers, W. R. Bishai, P. Goelet, and M. T. Boyce-Jacino. "Solid-Phase Sequence Scanning for Drug Resistance Detection in Tuberculosis." *Molecular and Cellular Probes*, 13: 81-87, 1999.
- Rogers, Y.-H., P. Jiang-Baucom, A.-J. Huang, V. Bogdanov, S. Anderson, and M. T. Boyce-Jacino. "Immobilization of Oligonucleotides onto a Glass Support via Disulfide Bonds: A Method for Preparation of DNA Microarrays." *Analytical Biochemistry*, 266(1): 23-30, 1999.
- Pohl, M.G., L. Picoult-Newberg, R. Patch, and M. Boyce-Jacino. "Primer Design for High Throughput Primer Extension." *American Journal of Human Genetics* 67 (4) 2000: 273, Suppl. 2.
- Donaldson, M.A., J. Lathrop, C. A. Gelfand, N. Nouri, T. Ryder, and M. Boyce-Jacino. "The SNPcode 100 Genotyping Kit: A Generic System for SNP Genotyping on High Density Arrays." *American Journal of Human Genetics* 67 (4): 273-273, Suppl. 2, 2000.
- Swenson, R. E.; Q. Xu, C. Gelfand, M. Donaldson, and M. Boyce-Jacino. "Polymerase Signaling Assay for DNA Sequencing and DNA Polymorphism Analysis." *American Journal of Human Genetics* 67 (4): 273-273, Suppl. 2, 2000.

# PROJECT HIGHLIGHTS
## Orchid BioSciences (formerly Molecular Tool, Inc.)


- Kunkel, M. A., C. A. Gelfand, J. Jacobson, and M. Boyce-Jacino. "Bead-based Determination of Single Nucleotide Polymorphisms by Primer Extension." *American Journal of Human Genetics* 67 (4): 273, Suppl. 2, 2000.
- Gelfand, C. A., R. A. Swenson, J. Tarantino, B. Hoghooghi, M. Pohl, F. Shemansky, G. Schnerr, and M. T. Boyce-Jacino. "The MegaSNPatron: An Ultra-high Throughput Genotyping Platform." *American Journal of Human Genetics* 67 (4): 273-273, Suppl. 2, 2000.
- Donaldson, M.A., J. A. Lathrop, W. M. Ankener, J. F. Studebaker, S. V. Alfisi, M. S. Philips, C. A. Gelfand, and M. T. Boyce-Jacino. "Simultaneous Genotyping of more than 1000 SNPs with the SNPcode (TM) Platform." *American Journal of Human Genetics* 69 (4): 470-470, Suppl. 1, 2001.
- Sundaresan, B.C., M. Xu, K. Davis-Fleischer, M. Phillips, P. A. Bell, and M. Boyce-Jacino. "Bench-top Genotyping Using a 96 Strip-well Primer Extension SNP-IT (TM) Assay." *American Journal of Human Genetics* 69 (4): 460, Suppl. 1. 2001.
- Mulcahy, T.M., M. A. Kunkel, D. Greeny, R. Liberchuk, A. Camisa, J. Studebaker, C. A. Gelfand, P. A. Bell, and M. Boyce-Jacino. "SNPstream (R) MT, a Microsphere-based, Primer Extension System for the Analysis of Single Nucleotide Polymorphisms." *American Journal of Human Genetics* 69 (4): 460, Suppl. 1, 2001.
- Bell, P.A., X. Zhao, E. Huang, C. Emerich, R. Zhao, J. C. Wu, S. Verde, D. Kahn, K. E. Scott, C. A. Gelfand, M. Ruben, F. Jones, K. Chokshi, P. Farnsworth, V. Bogdanov, R. Kopla, F. Modica, A. Recber, A. Yasseen, J. Tarantino, M. Kochersperger, A. Huang, F. S. Kuo, M. Pohl, G. Schnerr, and M. T. Boyce-Jacino. "Ultra-high Throughput Genotyping Platform Using Arrayed Glass Plates and Primer Extension." *American Journal of Human Genetics* 69 (4): 459, Suppl. 1, 2001.
- Studebaker, J., S. Alfisi, W. Ankener, D. Morris, and M. Phillips. "Automated Classification of SNP Genotyping Results." *American Journal of Human Genetics* 69 (4): 452, Suppl. 1, 2001.
- Phillips, M. S., V. M. Ankener, D. W. Morris, J. F. Studebaker, M. A. Donaldson, J. A. Lathrop, F. S. Kuo, A. V. Alfisi, G. A. Gelfand, M. G. Pohl, and M. T. Boyce-Jacino. "Determination and Analysis of > 30,000 SNP Allele Frequencies in Three Defined Populations and CEPH Pedigrees from SNPs Identified by the SNP Consortium." *American Journal of Human Genetics* 69 (4): 415, Suppl. 1, 2001.
- Scott, K. E., J. F. Studebaker, F. Kuo, M. S. Phillips, P. Bauer, W. A. Ankener, M. A. Donaldson, L. Cardon, and M. T. Boyce-Jacino. "A Genome-wide SNP Panel for Use in Mapping and Association Studies." *American Journal of Human Genetics* 71 (4): 463-463, Suppl. S, 2002.
- Varde, S.A., J. A. Lathrop, M. A. Donaldson, J. M. Maris, G. Hii, P. Fortina, E. Rappaport, W. M. Ankener, J. F. Studebaker, S. V. Alfisi, M. S. Phillips, M. T. Boyce-Jacino, and C. A. Gelfand. "Loss of Heterozygosity Studied Using SNPs as Markers." *American Journal of Human Genetics* 71 (4): 410, Suppl. S, 2002.
- Sundaresan, B.C., J. C. Mylet, T. Mulcahy, and C. Crego. "Genotyping with Orchid's SNP-IT (TM) Technology Using Singlex and Multiplexed Tag-based Platforms." *American Journal of Human Genetics* 71 (4): 409, Suppl. S, 2002.
- Gelfand, C. A., K. E. Scott, and S. A. Varde. "SNP Allele Frequency Determined for Pooled Samples in Multiplexed Assays." *American Journal of Human Genetics* 71 (4): 409, Suppl. S, 2002.
- Kunkel, M.A., J. Baisch, C. Barceleau, C. Y. Huang, and C. Gelfand. "Full Multiplexing of up to 48 SNP Genotypes on the SNPstream (R) UHT Genotyping System." *American Journal of Human Genetics* 71 (4): 406, Suppl. S, 2002.
- Mody, M., J. C. Mylet, M. J. Thomas, S. Varde, and C. A. Gelfand. "Effect of Multiplex PCR Conditions on the SNPstream (R) UHT Genotyping System." *American Journal of Human Genetics* 71 (4): 401, Suppl. S, 2002.
- Yuryev, A., J. Kuebler, M. Donaldson, K. Scott, J. Studebaker, J. Huang, M. Pohl, and M. T. Boyce-Jacino. "Primer Design and Marker Clustering for Multiplex Primer Extension SNP Genotyping Assay Using Statistical Modeling." *American Journal of Human Genetics* 71 (4): 393, Suppl. S, 2002.
- Marchini, J. L., P. Donnelly, M.T. Boyce-Jacino, and L. Cardon. "Assessing Population Structure and its Effects on Association Studies in a Genome-wide SNP Dataset." *American Journal of Human Genetics* 71 (4): 372, Suppl. S, 2002.